The role of autologous chondrocyte implantation in the treatment of symptomatic chondromalacia patellae

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Abstract

Purpose Chondromalacia patella is a distinct clinical entity of abnormal softening of the articular cartilage of the patella, which results in chronic retropatellar pain. Its aetiology is still unclear but the process is thought to be due to trauma to superficial chondrocytes resulting in a proteolytic enzymic breakdown of the matrix. Our aim was to assess the effectiveness of autologous chondrocyte implantation on patients with a proven symptomatic retropatellar lesion who had at least one failed conventional marrow-stimulating therapy.

Methods We performed chondrocyte implantation on 48 patients: 25 received autologous chondrocyte implantation with a type I/III membrane (ACI-C) method (Geistlich Biomaterials, Wolhusen, Switzerland), and 23 received the Matrix-assisted Chondrocyte Implantation (MACI) technique (Genzyme, Kastrup, Denmark).

Results Over a mean follow-up period of 40.3 months, there was a statistically significant improvement in subjective pain scoring using the visual analogue scale (VAS) and objective functional scores using the Modified Cincinnati Rating System (MCS) in both groups.

Conclusions Chondromalacia patellae lesions responded well to chondrocyte implantation. Better results occurred with MACI than with ACI-C. Excellent and good results were achieved in 40% of ACI-C patients and 57% of MACI patients, but success of chondrocyte implantation was greater with medial/odd-facet lesions. Given that the MACI

procedure is technically easier and less time consuming, we consider it to be useful for treating patients with symptomatic chondral defects secondary to chondromalacia patellae.

Introduction

Chondromalacia patella is a distinct clinical entity in which there is anterior knee pain and softening or breakdown of the articular cartilage on the medial and “odd” facet of the patella. Changes can also affect the lateral facet, especially if there is tightness of the lateral patellar retinaculum, as described by Ficat [1]. Many treatment methods have been proposed, including drilling, defect excision and proximal soft tissue and distal bony patellar realignment surgery [2]. Trochleoplasty [3, 4] has shown good results where femoral condyle dysplasia is suspected as the main cause for patellar instability. Longitudinal patellar osteotomy for anterior patellofemoral pain [5, 6] and patellectomy have also been described as modes of treatment, but none have been totally successful. Disease aetiology remains unconfirmed. Some consider it the result of malalignment of the unstable patella as it articulates with the distal femur [7]. This has now been largely discounted. Others propose that the cause is secondary to trauma to the articular cartilage where there has been a breakdown of articular cartilage and damage to superficial chondrocytes resulting in release of proteolytic lysosomal enzymes [8, 9]. Outerbridge [10] originally graded chondromalacia patellae as follows;

Grade I softening and swelling or fibrillation/fissuring in an area <0.5 cm;

Grade II fissuring or fibrillation/fissuring in an area 0.5–1 cm;

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Fig. 1 **a** Arthrotomy, with arrows exhibiting multifaceted chondromalacia patellae. **b** Same patient as in Fig. 1a; debrided lesion. **c** Same patient as Fig. 1a; Matrix-assisted Chondrocyte Implantation (MACI) graft in situ following cutting graft to appropriate size. **d** Infiltration of cultured cells beneath type I/III collagen membrane for large chondromalacia patellae lesions

- Grade III fibrillation (crabmeat appearance) or fibrillation/fissuring in an area 1–2 cm;
 Grade IV erosive changes and subchondral bone exposure or fibrillation in an area >2 cm.

This system has largely been superseded by the International Cartilage Repair Society (ICRS) chondral injury classification, as follows:

- Grade 0 normal;
 Grade 1 nearly normal (soft indentation and/or superficial fissures and cracks);
 Grade 2 abnormal (lesions extending down to <50% of cartilage depth);
 Grade 3 severely abnormal (cartilage defects >50% of cartilage depth);
 Grade 4 severely abnormal (through the subchondral bone).

The role of patellar malalignment in chondromalacia patella has been widely investigated. Femoral dysplasia (increased sulcus angle on radiographs) has been implicated in the pathogenesis. Aglietti and Cerulli [11] observed an increased sulcus angle in a group of patients with clinical signs of chondromalacia patella and those with normal knees. In contrast, Brattstrom [12], Merchant et al. [13] and Bentley and Dowd [9] found no correlation between a widened femoral intercondylar groove and chondromalacia patella based on both clinical and arthroscopic findings. It was believed that chondromalacia patella is a precursor to osteoarthritis; however, a 20-year clinical follow-up by Karlson [14] and cadaveric studies by Meachim and Bentley [15] suggest this is not the case. The exception is lateral facet chondromalacia patella, which is associated with a tight lateral patellar retinaculum and has been reported as preosteoarthritic [1]. Two thirds of patients affected by symptomatic chondromalacia patellae are

Table 1 Patient demographics

	All patients (n=48)	Group 1 (ACI-C) (n=25)	Group 2 (MACI) (n=23)
Females	71%	80%	61%
Males	29%	20%	39%
Mean age	34.8 (17–50)	34.6 (17–50)	35 (21–46)
Length of symptoms (months)	89.75 (6–336)	87.64 (6–216)	92.04 (17–336)
Number of previous procedures	1.94 (1–7)	1.8 (1–6)	2.09 (1–7)
Size of defect (cm ²)	4.75 (1–10.5)	4.73 (1–8.75)	4.76 (1–10.5)
Mean follow-up (months)	40.3	45	35.3

ACI-C autologous chondrocyte implantation with a type I/III membrane, MACI Matrix-assisted Chondrocyte Implantation

Table 2 Mean visual analogue scale (VAS), Bentley and Modified Cincinnati Rating System (MCS) scores pre= and postoperatively of entire cohort and of each subset

	All patients mean preoperatively (n=48)	All patients mean postoperatively	ACI group mean preoperatively (n=25)	ACI group mean postoperatively	MACI group mean preoperatively (n=23)	MACI group mean postoperatively
VAS (0–10)	6.42 (2–10)	4.5 (0–10)	6.32 (2–10)	5 (1–9)	6.52 (2.5–10)	3.96 (0–10)
Stanmore/Bentley (0–4)	2.92 (0–4)	2.27 (0–4)	3.04 (1–4)	2.44 (0–4)	2.78 (1–4)	2.09 (0–4)
Modified Cincinnati Score (6–100)	45.13 (18–75)	54.81 (11–100)	42.12 (18–60)	48.76 (11–83)	48.39 (22–75)	61.39 (8–100)

female [16] and symptoms affect two distinct groups. Some are inactive teenage girls, and others are highly active teenagers of both sexes [9]. The first group experience symptoms after long periods of knee flexion, e.g. when driving or sitting at a desk, and is commonly relieved by mobilising the knee joint. In the second group, symptoms are aggravated by sport and relieved by rest.

Clinical examination for chondromalacia patella is commonly unreliable. By far the most common feature is tenderness on palpation of the medial undersurface of the patella. Other, less convincing, signs are patellar crepitus, a positive apprehension test and effusion and pain on compressing the patella onto the distal femur. Leslie and Bentley [17] found the presence of quadriceps wasting of more than 2 cm at a distance of 6 cm above the patella and effusion in the knee to be a useful tool in aiding diagnosis. Magnetic resonance imaging (MRI) has proven to be extremely useful, and with the advent of delayed gadolinium-enhanced MRI of the cartilage (dGEMRIC) studies, identifying subtle chondral lesions of the patellar is possible [18]. Despite advances in imaging of the knee, arthroscopy remains the gold standard for diagnosing chondromalacia patellae.

Surgical treatment of this condition has varied over time. Bentley [19] reviewed the results following patellar tendon transfer, cartilage excision and drilling, shaving and patellectomy. He found that careful consideration must be made in selecting patients for the correct procedure. Adolescents and athletes with grade I, II or III changes would benefit from patellar tendon transfer with lateral release and medial reefing. Older adults with grade I or II disease benefitted from cartilage excision and bone drilling, whereas adults with grade III or IV disease benefitted from patellectomy. Other procedures, such as those described by Macquet and Fulkerson [20, 21], that advance and medialise the tibial tuberosity have also been reported as successful. Trochleoplasty, as described by Dejour [3], and proximal soft tissue realignment surgery, such as medial patellofemoral ligament

reconstruction, have also yielded good results [22]. There are also reports of direct treatment of painful articular sites with carbon fibre implants [23], with a 41% patient satisfaction rate; mosaicplasty [24] and the use of autologous chondrocyte implantation.

In this study we reviewed a cohort of patients who underwent cartilage implantation either with autologous chondrocyte implantation (ACI-C) or Matrix-assisted Chondrocyte Implantation (MACI[®]) (Genzyme, Kastrup, Denmark).

Patients and methods

This study was approved by the joint research and ethics committee of the Hospital Trust. We reviewed 48 patients from August 1999 to April 2006 who were identified from larger prospective cohort studies and who underwent chondrocyte implantation by either of ACI or MACI. Choice of implantation technique was based on lesion size and site. Each patient was referred to our unit with a chondral or osteochondral defect secondary to chondromalacia patellae and were assessed clinically. Pain and function were

Table 3 Percent of excellent, good, fair and poor Modified Cincinnati Rating System (MCS) functional results

MCS	ACI [n (%)]	MACI [n (%)]
Excellent (≥80)	4 (16)	6 (26.1)
Good (55–79)	6 (24)	7 (30.4)
Fair (30–54)	6 (24)	8 (34.8)
Poor (<30)	9 (36)	2 (8.7)
Total	25	23

The proportion of patients that achieved excellent and good results in the autologous chondrocyte implantation with a type I/III membrane (ACI-C) group was 40% compared with 56.5% in the Matrix-assisted Chondrocyte Implantation (MACI) group

ACI-C autologous chondrocyte implantation with a type I/III membrane

Fig. 2 Mean Bentley scores with confidence intervals and *p* values

measured using the visual analogue scoring (VAS) (0–10), Modified Cincinnati Score (6–100) and Stanmore/Bentley functional scoring systems (0–4). All patients had at least one previous operation on the affected knee and consented to take part in the study. Each patient was treated by a two-stage procedure. The first stage was an arthroscopy to confirm the diagnosis and assess lesion size and site. Patients were either allocated to ACI or MACI. A cartilage biopsy was harvested from a non-weight-bearing area for culture. The biopsy was sent to the laboratory where chondrocytes were cultured for four to six weeks, after which patients were readmitted for arthrotomy (Fig. 1a). The lesion was debrided to stable cartilage (Fig. 1b) followed by implantation of chondrocytes either in the form of MACI or ACI-C. The limb was then placed in a posterior splint, which was converted to a cylinder cast, and were discharged fully weight-bearing, with crutches to aid balance and reduce potential shearing forces, which might prevent the graft from taking. Ten days postoperatively, the plaster cast was removed and an intensive physiotherapy regime instituted.

Fig. 3 Mean visual analogue scale (VAS) scores with confidence intervals and *p* values

MACI involves cells that have been preseeded onto a type I/III collagen membrane with a density of 1×10^6 cells per cm^2 and glued in situ over the defect using fibrin glue (Fig. 1c) (Tisseel; Baxter, Vienna, Austria). ACI-C involves implantation of cultured cells beneath a collagen type I/III membrane, which has been sutured into position using 6/0 absorbable sutures (Fig. 1d). Patients were followed up at six weeks, six months and one year postoperatively and subsequently on an annual basis. Each year, patients were rescored on the VAS, Cincinnati and Bentley scoring systems. Return to full sporting activity was permitted at one year.

Statistical analysis

SPSS (version 14.0; SPSS Inc., Chicago, IL, USA) was used to perform all statistical analysis. The paired *t* test was used to compare functional scores before and after surgery. The two sample *t* tests (with normal variances assumed) was used to compare the change in scores between the ACI and MACI groups. Fisher's exact test (two-tailed significance) was performed to compare results.

Results

Table 1 shows patient demographics and lesion characteristics in the entire study group and the specified subdivisions. Table 2 shows the mean pre-and postoperative scores in the entire study cohort and the specified subdivisions. Table 3 exhibits post operative functional scores using the MCS.

Figures 2, 3 and 4 display pain and functional scores before and after surgery. Although the follow-up period was longer in the ACI group, this was not statistically significant ($p = 0.08$). There was a significant improvement in function as assessed by all three scoring systems in the overall group and in the MACI group.

Fig. 4 Mean Modified Cincinnati Rating System (MCS) scores with confidence intervals and *p* values

Although the MCS increased in the ACI-C group (by 6.7 points), this was not statistically significant. When comparing outcomes of ACI-C and MACI directly, there was no statistically significant difference in the change in MCS, VAS and Bentley scores. MCS at latest follow-up was considerably lower in the ACI group (48.8) compared with the MACI group (61.4). Though this was not statistically significant, the p value was low ($p=0.07$), which suggests that there may be a trend and that if the study was adequately powered, a significant result would be obtained. The proportion of patients who achieved excellent and good results in the ACI-C group was 40% compared with 56.5% in the MACI group.

Site of chondromalacia patellae on the patella

Of the entire cohort, the site of the patella affected by chondromalacia was documented. Of those 20 documented cases affected the medial/odd facet, 13 affected the lateral facet and 15 were multifaceted disease: ACI group, eight medial facet, six lateral facet and 11 multifaceted; MACI group, 12 medial facet, seven lateral facet and four multifaceted. Table 4 shows the post operative functional scores based on the site of patellar lesion using the MCS.

Medial-facet lesions had statistically significant excellent and good results compared with lateral lesions ($p=0.029$). Similarly, medial lesions did better than multi-facet lesions ($p=0.007$), though there was no difference between lateral and multifaceted lesions ($p=1.0$). Ficat et al. described “excessive lateral pressure syndrome” of the patella with a tight lateral retinaculum [1]. Bentley and Dowd proposed that this type of chondromalacia patellae of the lateral facet is, in fact, early and progressive osteoarthritis [9]. This may well explain the poor results of the lateral-facet and multifacet patellar cases.

Discussion

To our knowledge, this is the first report of patients who have received autologous chondrocyte implantation for symptomatic chondromalacia patellae. ACI was first described, in 1994, by Brittberg for treating osteochondral or

chondral lesions of the femoral condyles and also in a small number of patellar lesions [25]. Nevertheless, lasting benefits of this treatment have been reported up to 11 years [26]. Chondrocyte transplantation has also shown superiority over other forms of treatment for symptomatic osteochondral lesions of the knee [27, 28]. This presented an alternative treatment for chondromalacia patellae sufferers who had not fared well with previous modes of surgical treatment. Minas et al. described the role of AC I-C in the patellofemoral joint and found that 71% of patients had good or excellent results [29]. However only eight of the chondral lesions were confined to the patella. Analysis by Krishnan et al. [30] suggested that patellar chondral lesions do not respond as well to chondrocyte implantation as other sites within the knee. Our results confirm this, with fewer good and excellent results compared with lateral femoral condyle and trochlear lesions.

In this study, which was confined to patellar defects of large size, both treatment methods exhibited a statistically significant improvement in function and subjective pain scores. However, it appears that MACI patients achieved better results than their ACI-C counterparts, although the ACI-C patients tended to have more complex lesions. Our study further suggests that over the medium term, MACI provides greater symptomatic relief and functional outcome than does ACI-C, although this is not statistically significant. The MACI group did, however, have a slightly shorter follow-up period. Another potential confounding factor is the site on the patella affected by chondromalacia patellae. We observed from our cohort that patients with medial patellar disease had a better outcome than those with lateral and multifaceted disease. The ACI-C group had almost twice as many lateral and multifaceted lesions compared to the MACI group. There is evidence to suggest that lateral chondromalacia patella is in some cases early osteoarthritis [15], and as the ACI-C group had more lateral and multifaceted lesions, this could also explain the poorer outcomes.

Radiographic analysis

During this study, we assessed the available preoperative X-rays of the knee in 23 patients. Lateral radiographs performed in flexion were assessed for patella alta using the Insall/Salvati

Table 4 Percent of excellent, good, fair and poor results based on site of patellar lesion

Mean Modified Cincinnati Rating Scale	Lateral facet [n (%)]	Medial/odd facet [n (%)]	Multifaceted [n (%)]
Excellent (≥ 80)	1 (8)	7 (35)	2 (13)
Good (55–79)	3 (23)	8 (40)	2 (13)
Fair (30–54)	5 (38)	3 (15)	6 (40)
Poor (<30)	4 (31)	2 (10)	5 (34)

ratio [31]. We found in our series that the presence or absence of patella alta had no bearing on the clinical outcome following chondrocyte implantation. The sulcus angle [13] was also assessed on skyline and tangential views, and again, the presence or absence of an increased angle ($>139^\circ$) appeared to have no bearing on final functional outcome in either group. This is in contrast to studies by Aglietti and Cerulli [11] and Lancourt and Cristini [32].

Treatment of primary lesions

We observed that our patients suffering from symptomatic chondromalacia patella had all had surgical procedures prior to being referred to our unit for cartilage transplantation. This is a consequence of the National Institute for Health and Clinical Excellence (NICE), UK, guidelines that advise against the use of chondrocyte implantation for symptomatic chondral lesions as a primary treatment [33]. Thus patients' symptoms were, on average, of 7.5 years in duration prior to referral, which led to poor knee function with associated quadriceps wasting and significant pain leading to low morale. Also, all patients had at least one unsuccessful surgical treatment of their chondromalacia patella lesion in the form of debridement, chondroplasty or microfracture. A previous study from this unit [30] looked at the prognostic factors that indicated ideal candidates for ACI-C and concluded that low preoperative scores resulted in poorer outcome, as did extended history. These factors are obvious in this group of patients with chondromalacia patellae.

We conclude that symptomatic chondromalacia patellae lesions improved with chondrocyte implantation, especially in patients who received MACI. The longer a patient has symptoms and the more previous procedures, the worse the prognosis appears to be. Patients had on average a seven year history and were often at a point where symptoms were severe, with constant pain and significant reduction in function. We consider that earlier intervention could have provided even better results in this often difficult group of patients. However, a larger study is needed to clarify this point.

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